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Book of Abstracts

P27 Differential effects of chaperones and protein-sorting factors on yeast [PSI+] and [URE3] prions

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Prions in yeast Saccharomyces cerevisiae are heritable genetic determinants represented by self-perpeturating protein aggregates. Yeast prions propagate in cell lineages due to tight interaction with the protein quality control (PQC) machinery, i.e. chaperones and protein-sorting factors. In our work we undertook an effort to systematically assess the effects of a set of PQC components on the most studied yeast prions, [PSI+] and [URE3]. The main PQC component that confers propagation of all known yeast amyloid prions is the hexameric ATPase Hsp104 that is required for fragmentation of amyloid fibrils. We show that, despite frequent statements in the literature, overproduction of Hsp104 cures both [PSI+] and [URE3]. On the other hand, overexpression of the SSA1 gene, which has previously been reported to destabilize [URE3], had no significant effect on its propagation in our system. We also demonstrate that overproduction of the chaperone-sorting factor Cur1 cures [URE3] while enhancing [PSI+]. We link these effects to the relocalization of the Hsp40-Sis1 into the nucleus and show that Cur1-independent changes in Sis1 localization also oppositely affect [PSI+] and [URE3] propagation. We also show that, similarly to Cur1, overproduction of the other major cytosolic Hsp40, Ydj1, enhances [PSI+]. On the basis of these observations, we propose a model for such differential effects of the Hsp40 on yeast prions. We suggest that changes in the cytosolic balance of different Hsp40, i.e. Ydj1 and Sis1, oppositely affect propagation of [PSI+] and [URE3] due to different dependence of these prions on two distinct activities of the Hsp104 machinery, i.e. fibril fragmentation and aggregate malpartition. Our results provide new insights into the interplay between yeast prions and cellular PQC system and highlight the importance of intracellular chaperone balance for prion propagation.

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